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AUTHOR Brent, Robert L.
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ABSTRACT

This report discusses the magnitude of the problem of birth defects, outlines advances in the birth defects field in the past decade, and identifies those areas where research is needed for the prevention, treatment, and management of birth defects. The problem of birth defects has consumed a greater portion of our health care resources because of the reduction of infectious diseases and our ability to salvage and care for many malformed children. These health care costs are estimated conservatively at \$20 billion per year. For every 1000 live births, 130 have genetic or anatomical defects. A genetic etiology accounts for 25 per cent of anatomical defects. The largest group of defects (65 per cent) is believed to be polygenic or multifactorial in origin. Contrary to the notion that the main causes of birth defects are environmental agents such as drugs, chemical, and/or ionizing radiation, information gathered in the last 20 years indicates that these environmental agents account for only 10 per cent of birth defects. During the past decade, a greater prevention of birth defects has resulted from epidemiologic surveillance, better management of maternal medical disorders and obstetric and neonatal factors, greater understanding of the role of environmental factors and genetic diseases, insights obtained from psychosocial observations, and legal and ethical opinions. However, although much has been achieved during the last decade, many areas still need to be investigated. The improved management of maternal disease states and the development of vaccines or effective treatment of intrauterine infections are areas for maximal investment of future resources. (Author/MP)

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MATRIX NO. 2

BIRTH DEFECTS

by

Robert L. Brent, M.D., Ph.D.
Professor and Chairman
Department of Pediatrics
Jefferson Medical College

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BIRTH DEFECTS

The Magnitude of the Problem of Birth Defects

The broad definition of a birth defect is "an anatomical, physiological or biochemical abnormality that is present at birth." This, of course, would include both genetic and environmental diseases. In some instances, such as cystic fibrosis or Huntington's chorea, the disease may not be manifested for years. Birth defects are an important component of reproductive failures, which also includes abortions and stillbirths. The magnitude of the problem may be summarized as follows:

Minimum number of conceptions to obtain 1000 live births	1350
Abortions per 1000 live births	350
Anatomical malformations/1000 live births	30
Genetic disease total/1000 live births	100

Thus, for every 1000 live births, there are 130 children born with a significant defect and a substantial number of conceptions that never reach term. It is obvious that human pregnancy has a high failure rate, and therefore, is quite an imperfect process. In fact, the high spontaneous abortion rate includes a significant proportion of chromosomally abnormal embryos. The anatomical malformations referred to by many as "birth defects" or "congenital malformations" are best known to the public. These malformations include:

1. Anencephaly, spina bifida and other CNS defects
2. Congenital heart disease
3. Eye and ear malformations
4. Cleft palate and cleft lip
5. Limb reduction defects, club feet and other musculoskeletal malformations
6. Respiratory tract malformations
7. Gastrointestinal malformations
8. Genitourinary malformations
9. Congenital tumors
10. Syndromes (cytogenetic, genetic and nongenetic)

Since the thalidomide tragedy, the mistaken notion, among the public and even some scientists, is that the main causes of birth defects are environmental agents such as drugs, chemical and/or ionizing radiation. Although we still have much to learn about the causes of birth defects and the mechanisms involved in their development, we have developed information in the past 20 years that indicated that most anatomical malformations are not caused by environmental drugs and chemicals.

The breakdown on etiology is:

<u>Genetic</u>	<u>Per 100 Malformations</u>
Cytogenetic abnormalities	5%
Autosomal inheritance	20%
Polygenic, Multifactorial (and some unknown causes as well as spontaneous malformation caused by inherent mistakes in the processes of embryonic development)	65%

Environmental

Maternal disease states (Diabetes, maternal phenylketonuria, nutritional problems, smoking, alcoholism, etc.)	4%
Infections	3%
Constraint and constriction (mechanical)	1-2%
Drugs, chemical, irradiation, heat	1%

The custodial costs and medical management costs for this group of diseases are staggering. As an example, the cost of medical care for the children born with congenital heart disease each year is more than \$200,000,000. The custodial care for surviving children with cytogenetic defects born each year will amount to \$750,000,000 for their lifetime institutional care. If one includes the genetic diseases as well as the anatomical diseases, the medical care costs and custodial costs represent an annual cost of \$20 billion. This, of course, does not include the misery, pain and suffering of the affected children and their families.

Advances in the Birth Defects Field in the Past Decade

The fields that have contributed to a better understanding, better management of the prevention of birth defects are:

1. Epidemiology
2. Management of maternal medical disorders
3. Management of obstetrical and neonatal factors
4. Environmental factors
 - a. nutrition
 - b. drugs and chemicals
 - c. irradiation
 - d. infection
 - e. miscellaneous
5. Genetic diseases
6. Psychosocial issues
7. Legal and ethical opinions

1. Epidemiologic Surveillance. During the past 10 years, epidemiologic surveillance of congenital malformations has come of age. The Center for Disease Control in Atlanta established the Congenital Malformation Surveillance Branch in 1967. This operation has been expanded to include many regions of the country. These studies provide information about the ongoing incidence of birth defects. When allegations were made that particular agents may be teratogenic, these epidemiologic groups have been able to demonstrate that the allegations were not accurate. This has occurred with several alleged teratogens; the most recent, Bendectin.

The discovery that Warfarin and diethylstilbesterol were associated with an increase in developmental effects was made by alert physician epidemiologists in the past decade. While other allegations have been made in error by alert physicians, the increased resources of the larger epidemiologic programs can test the views of alert physicians by examining clusters or by establishing specifically designed epidemiological studies.

2. Management of Maternal Medical Disorders. The period of life when women are able to conceive has a low incidence of disease, and, therefore, serious medical problems occur in only a small proportion of pregnancies. These diseases are not only threatening to the viability and normalcy of the offspring but also may contribute to maternal morbidity and mortality. Some of these diseases are serious enough that some might question the prudence of becoming pregnant, but in a free society, we have not yet placed restrictions on the matter of pregnancy, even in cases where the mother and infant are at great risk because of the mother's medical problems. Even educational programs have not been widespread enough to make the general public aware of the impact of many diseases on the pregnant woman and her conceptus.

Better management of toxemia of pregnancy has decreased the occurrence of eclampsia and the complications of this disease. The improvement of the care of a host of complicated chronic diseases has permitted many of these women to become pregnant, and, therefore, has increased the incidence of high risk or complicated pregnancies.

It is of interest that it was the group of women with artificial heart valves who were receiving anticoagulants that created the cluster of *Warfarin babies*, thus permitting the identification of the Warfarin syndrome in affected babies.

The management of pregnant patients with glomerulonephritis, pyelonephritis, polycystic kidneys, nephrolithiasis, kidney malformations and kidney transplants presents unique and sophisticated problems in management.

Similarly endocrinopathies, diabetes, hematologic disease (anemia, lymphoma, leukemia, thromboembolism, coagulation defects, isoimmunization), collagen diseases, liver decompensation and malabsorption all present serious problems to the mother and the offspring. Furthermore, not only is the management difficult, but in some instances the therapy, while of benefit to the mother, may be a hazard to the embryo.

As mentioned before, pregnant women with these diseases account for less than 10% of all pregnancies, but the economic cost and consumption of professional time to manage these patients are considerable. Furthermore, infant normalcy, growth, and survival are reduced.

This group of patients demands unique and specialized skills and experience that are not available in every community hospital. There is little question that, once such a patient has decided to carry her pregnancy to term, she and her baby would benefit from specialized care. A decrease in the maternal and infant morbidity and mortality caused by these diseases would result from optimal medical treatment. But far better results would be obtained if the diseases could be prevented in the mother, or if the mother were aware of the medical consequences of pregnancy, so that she could make an intelligent decision with regard to becoming pregnant. Intermediate success can be achieved, by rigorous medical screening during pregnancy, for a large number of potentially hazardous conditions. The screening procedures are time consuming and extensive, and involve a large number of personnel from many disciplines. The early detection of disease, their vigorous management, and the opportunities for

patient education and family contact support the contention that the antenatal period is a most opportunistic time to practice this form of preventive medicine.

3. Management of Obstetric and Neonatal Factors. There has been a revolution in obstetrical perinatal care and pediatric neonatal care in the past 10 years. The development of the concept of *high risk* pregnancies and high risk centers, as well as the development of electronic monitoring equipment and ultrasonic diagnostic equipment have revolutionized this field.

Techniques of alpha fetoprotein analysis, amniocentesis, fetoscopy, fetal surgery and fetal therapy have contributed to the survival of newborns as well as resulting in a population of infants needing a higher degree of intensive care and having more morbidity and mortality.

The advances in the field of fetal diagnosis have presented the medical field with the difficult moral dilemma of how best to use this information for the health and welfare of the nation. One of the major advances in the past decade, regarding the matter of anatomical malformations, has been in the area of pediatric surgery. Infants with omphaloceles, congenital heart disease, esophageal atresia and many others now survive major surgical procedures, which frequently can completely correct defects. The morbidity and mortality has been decreased and the programs improved for many anatomical malformations.

4. Environmental Factors. a. Nutrition. There has been a refinement of our understanding of fetal growth and nutrition. While we recognize that embryonic and fetal disease are associated with maternal malnutrition, we recognize that fetal and embryonic malnutrition may be caused by intrinsic diseases of the placenta and embryo, such as cytogenetic abnormalities, placental disease, twinning, toxic drugs, multiple pregnancies, rare clinical syndromes, high dose radiation, inherited factors and certain maternal disease states.

Optimal nutrition is less likely to occur in a low socioeconomic population in this country as well as in many impoverished nations.

Within the past 10 years, the obstetricians have relaxed somewhat their restriction on food intake and weight gain during pregnancy on the advice of the Nutrition Committee of the National Academy of Sciences.

The field of nutrition research is in reality very complex biochemistry. Until we know the essential nutritional components that are necessary for normal embryonic development, we will not be in a position to describe adequately the optimal nutritional environment for the human embryo and fetus. These factors include, not only the limits of protein, carbohydrate, fat and vitamins, but also trace elements, specific amino acids and other biochemical constituents of the diet.

b. Drugs and Pharmacokinetics: The two important discoveries of new embryopathic agents in the 1970s are the effects of diethylstilbestrol and the *Warfarin syndrome produced by oral anticoagulants*. The fact that diethylstilbestrol produces adenosis and a low incidence of genital anatomical defects is less important than association of this drug with the occurrence of adenocarcinoma of the vagina. A larger group of other drugs have been alleged to be teratogens. Most have been shown not to be teratogenic in the human. Others are still being evaluated.

Administration of therapeutic drugs during the first third of pregnancy does not appear to account for more than a very small percentage of human embryotoxicity. It is concluded, however, that present methods for evaluating risk of new drugs may not be adequate to prevent another teratological catastrophe, and that the degree of teratogenic interaction between drugs and other environmental factors or between drugs and unstable genetic loci is not known.

Other drugs have been found useful in the treatment of the fetus or for the prevention of disease. The best example is the use of corticosteroids to reduce the incidence of respiratory distress syndrome by increasing the biochemical maturation of the lung. Active investigation has continued in the use of drugs to prevent prematurity, which certainly will result in a marked decrease in neonatal mortality and morbidity.

c. Irradiation. The most recent data indicated that levels of x-irradiation exposure during diagnostic procedures have a negligible risk to the developing embryo. Many physicians and lay individuals are misinformed about the consequences of diagnostic irradiation. It is paramount that physicians and the general population be better informed about the actual risk to the embryo of 1 rem exposures. Many unnecessary therapeutic abortions could be avoided if the risk of embryonic exposure were evaluated properly.

d. Infection. Malformations, embryonic death and severe disease in newborns may result from a number of maternal infections or carrier states during the embryonic or perinatal periods. Three viruses that infect the human fetus and produce embryopathology are well recognized: rubella, cytomegalovirus and herpes simplex. Recent findings indicate that several additional viruses must be added to the list: Venezuelan equine encephalitis virus, varicella-zoster virus, and Coxsackie virus. At least six other viruses are transmitted to the fetus and have the potential for producing death and disease.

An important cause of intrauterine bacterial infection is the spirochete that causes congenital syphilis.

In the perinatal period, many bacterial organisms may cause death or permanent disability. Furthermore, these bacteria are frequently part of the mother's normal flora. The organisms most commonly involved are the gram negative enterobacteriae, *Staphylococcus aureus*, hemolytic and nonhemolytic streptococci, and the gonococcus. The prevention and/or treatment of this group of infections involves epidemiologic bacterial surveillance, alert nursing and physician observation, and responsible diagnostic and therapeutic procedures.

Toxoplasma gondii is a protozoan intracellular obligate parasite. It is an ubiquitous organism and infects many mammals and birds in addition to man. Twenty percent of infected newborns have significant embryopathology. These include microcephaly, microphthalmia and hydrocephaly. The prognosis in congenital toxoplasmosis is extremely poor: approximately 12% die and 85% are mentally retarded.

Although we are not certain of how important intrauterine infections are to the total frequency of embryopathology, we do know that perinatal infections contribute significantly to the morbidity and mortality of the newborn.

e. Miscellaneous. After having reviewed the many known causes of embryonic fetal and perinatal diseases, we are left with two very difficult questions: (1) What fraction of fetal and perinatal disease is caused by environmental hazards? (2) What other maternal or environmental factors have been invoked as embryopathic agents? Genetic diseases are the largest single known cause of human embryopathology, but in many instances, the etiology of altered cytogenetic condition is unknown. Multiple factors may be very important in the etiology of human malformations. The multifactorial hypothesis contends that many environmental factors may act synergistically in producing embryopathology. Yet, when these factors are evaluated separately, they appear to be innocuous to the embryo.

The largest category also consists of a group labeled "biologic errors inherent in the reproductive and developmental process, similar to the concept of spontaneous mutations." Some have referred to this as "developmental noise," meaning that if the environment were optimal, embryopathology still would occur, because the reproductive and developmental processes have a built-in probability of going awry. If this interpretation is correct, then embryopathology never may be reduced to zero, unless we develop a technique that prevents abnormal embryos from reaching term.

The fact that many malformations may be caused by the intrinsic failure rate of the developmental process should not deter us from searching for other preventable causes of human malformations. Within the past decade, there has been a marked increase in the exposure of human embryos to microwave radiation and ultrasound. Although preliminary studies indicate that the present maximum permissible exposures are safe for the embryo, further studies are being undertaken.

Other potential or proven embryotoxic situations include maternal hyperthermia, intrauterine constraint, and constriction (uterine abnormalities, amnionitis, bands, cord compression), maternal alcoholism, and maternal smoking.

The subject of miscellaneous or controversial causes of malformations is discussed at length by several authors (Brent & Harris, 1976; Wilson, 1973).

Genetic Diseases

Genetic diseases are common in developed Western societies where infectious and nutritional diseases have decreased in frequency. Genetic diseases include the various chromosomal aberrations, mendelian disorders caused by single gene mutations, such as hemolytic diseases of the newborn caused by Rh incompatibility and polygenic diseases.

The most common chromosomal disease is Down's syndrome or trisomy 21, which usually is not inherited, but is caused by a mishap in cell division before or shortly after fertilization. There are over 1000 mendelian disorders; each of these usually is rare, but these diseases, in the aggregate, are not uncommon. Many recessive and some X-linked diseases are caused by mutations affecting enzyme function. The basic defect in autosomal dominant rarely is known. Rh disease of the newborn is rather frequent and can be prevented by appropriate immunologic therapy of the prospective mother. The greatest impact of genetic disease probably relates to multifactorial disease (10% of all births). These include many congenital malformations

(such as spina bifida and cleft palate), the common psychoses of adults (such as schizophrenia and manic-depressive disorders), and many common diseases of adults (such as high blood pressure, diabetes, arteriosclerosis and peptic ulcer). Accumulating data on the role of genes in disease etiology suggest that genetic factors play a role in most diseases. Even discounting the polygenic disorders, clear-cut genetic disorders contribute heavily to the total disease load of our population.

A significant proportion of cases of deafness (50%), blindness (50%), and mental retardation (25%) is caused by genetic factors. The total impact of these disabilities is significant.

Approaches to the management of genetic diseases may not differ from treatment of other diseases. For many genetic diseases, dietary, medicinal, and surgical therapies may apply. The results may be corrective, remedial or palliative. Since genetic diseases have the added burden of recurrence in future offspring or the next generation, advice regarding such risks and the various problems surrounding the severity and natural history of the disease need to be provided. The field of *genetic counseling* is growing and as the role of genetics in the etiology of disease increases, more and more parents demand such services. Most genetic counseling centers have been established in medical schools but now are being extended to less specialized settings in the form of *outreach clinics* and similar facilities.

The feasibility of intrauterine diagnosis by amniotic puncture for all chromosomal and many metabolic genetic diseases allows positive identification of affected or normal fetuses and selective abortion. The procedure appears safe and is used increasingly in the management of genetic disease.

Screening for genetic diseases is becoming more feasible. Screening may be performed in order to detect affected individuals for treatment, such as in phenylketonuria. Screening also may be useful to identify genetic carriers prior to procreation, such as in sickle cell anemia and Tay-Sachs disease. Genetic counseling services must be provided with such programs.

There are many possibilities regarding future management of genetic diseases. Enzyme therapy, substitution of missing proteins, and molecular manipulation of variant proteins already are possible for a few diseases. Intrauterine therapy may be possible in some instances. Increasing understanding of the chemical, cytologic, and immunologic basis of genetics allows for prevention and/or treatment of an increasing number of genetic diseases. Replacement of mutant enzymes occasionally may be feasible by gene therapy, since some human genes already can be isolated. Their introduction into the affected cells poses greater difficulties.

Psychological Aspects

Effective prevention of fetal, perinatal and developmental disorders requires the application of information from multiple viewpoints. These include not only biological and statistical-epidemiological but also psychosocial approaches. In studying such disorders, psychosocial observations pertain to (1) causal and contributing factors, (2) the impact and consequences of defects for individuals, families and society, and (3) the effective delivery and utilization of therapeutic and preventive

services. Regarding causal factors, there is evidence that psychosocial variables, such as maternal anxiety levels and psychological experiences during pregnancy, are associated with complications of pregnancy and low birthweight. Other recent work suggests that the earliest contacts between mother and newborn infant may influence profoundly their subsequent relationships, and, consequently, the infant's development. Furthermore, psychological variables may be the sole expressions of some developmental disorders. These are manifested primarily by disturbances of mental functioning without obvious somatic defects. Such disorders consist of a spectrum of impaired intellectual functioning from severe mental retardation to *minimal brain dysfunction* and also a cluster of psychiatric syndromes, such as hyperkinetic disorders, autism and perhaps schizophrenia.

The consequences of developmental defects require further delineation in psychosocial terms even if the available behavioral concepts and data are less quantifiable than measures of incidence and prevalence of defects. A variety of behavioral concepts is available to understand the impact of defects. Operationally most useful are the concepts describing psychological patterns of loss, mourning and giving-up in relationship to the family's disappointment over not having the anticipated ideal child. The concept of stigmatization is another example of a heuristically promising framework to understand the defective individual whose real traits deviate from expected ones. The application of such concepts in organizing psychosocial observations will contribute significantly to necessary research on the consequences of defects and to the development of therapeutic services.

Within the broader array of defects, the goal of prevention is most promising in the case of clear genetic disorders. Clinical genetics, as applied in genetic counseling, involves therapeutic and preventive endeavors that could serve as a paradigm of all health counseling. Genetic counseling involves the bilateral transfer of information in a developing relationship. This transaction almost always occurs in a highly emotional setting caused by a recent distressing experience with a defective child, so that psychosocial issues will critically influence the effectiveness of such counseling. Behavioral variables will determine the completeness and accuracy of the diagnostic data obtained, the counselee's responsiveness to the information transmitted by the counselor, and the subsequent plans and actions of the counselees. While these psychological issues in counseling are recognized, the necessary studies of their influence remain to be done. For example, it is necessary to compare differing standardized techniques of counseling regarding outcome in terms of information retained, comprehension, changes of attitudes, plans and future reproductive behavior. Each of these outcome parameters for each technique must be studied in relationship to differences among counselees. Counselees may be grouped and characterized according to personality style, family structure, educational levels, economic factors and religious practices. The risk of adverse outcomes, such as increased anxiety or massive denial of information, also must be assessed for each counseling technique and situation, for each group of counselees, and for the degree of psychologic stress experienced by individuals as they seek counseling.

Presently available studies are inadequate to detect the incidence, prevalence or course of psychologic distress involved in entering counseling following the birth of

a defective child. Such distress may be manifested in the form of persistent mood or somatic and/or social changes. Both for the design and data collection of the needed research, and, also, for the management of these forms of distress, it will be necessary for the counselor to possess some of the skills and experience of psychological medicine.

Legal Aspects

The rapid advances in the biologic and medical aspects of fetology and perinatology have been associated with equally rapid changes in the legal and ethical considerations surrounding these fields. The relative ease of contraception and abortion establishes birth as a far more designed and contrived process than the happenstance, good fortune or misfortune it once was considered to be. In this light, the scientific prevention and management of fetal and perinatal disease demands not only the specific applications of the biologic and medical disciplines, but the support and protection of our institutions.

Fetology and perinatology have unique legal and ethical considerations, including abortion, intrauterine diagnosis, implications of genetic counseling, prenatal injuries, and clinical research. Added to these unique considerations is the impact of the women's movement and the regulation of some kinds of fetal research.

The present legal and ethical considerations will not remain static, for although the law and our legal system constitute the expressed intent of the people, the expressed intent has changed dramatically over the past 30 years. Although the ethical tenets are the first to be cited, they are frequently the last to be observed.

Ethical, legal, or medical considerations by themselves cannot solve the present questions pertaining to malpractice, fetal research, the rights of the fetus, abortion, contraception, the right to health care, genetic counseling, genetic engineering and maternal rights. Over the next decade, new laws will be written and tested, the public's ethical considerations will change, and the results will influence greatly the health and welfare of future generations of Americans. The process is likely to be painful and divisive. In our democratic society, there is every likelihood that the process will succeed, and that our society will be better as a result of this maturation.

As ethical issues are brought into the open, they become part of the public domain. Widespread debate may induce dispute based on such concerns as societal responsibility versus individual needs and rights, privacy relative to state interest, and respect for life and death within the pursuits of knowledge. These differences call for new advocates and better ways to decide among conflicting values and obligations.

Research Needed in the 1980s for the Prevention, Treatment and Management of Birth Defects

An extensive and high quality program in biomedical research is an essential investment for future health care developments. Our nation, which understands the importance of capital investment, must maintain a significant portion of the biomedical research effort in the broadest categories. Since goal-oriented research has narrow limits for success, we must be careful not to invest too many of our scientific

resources in narrow goal-oriented projects, and, therefore, prevent the development of broad based scientific knowledge from which most clinical advances are derived.

Fundamental investigations in the area of embryology and developmental biology are essential in providing the scientific base from which to branch out to attempt to solve the specific problems of prenatal and perinatal disease. Without the knowledge of structure and function of embryonic cells, tissues and organs; without an understanding of maternal physiology and feto-maternal relationships; and without information concerning the expression or repression of genetic information of the developing fetus; it would be difficult, if not impossible, to map a strategy of attack on the individual pathological manifestations of development.

It is the nature of research that its execution frequently precedes the recognition of its significance in the solution of specific problems. Even if only for this reason, the support of research and the training and support of individuals who will carry out that research seems to us of paramount importance in the establishment of any long-range program designed to prevent fetal and perinatal disease.

1. Further description of the morphological details of human embryology, especially with the techniques of electron microscopy, histochemistry and cytochemistry, as well as utilization of in vitro techniques to study human embryonic cells, tissues and organs. Use of these same techniques in studies on normal differentiation and growth in nonhuman embryos, especially in those forms most commonly used for experimental work.

2. Re-employment of the classical techniques of extirpation and transplantation along with the use of a variety of environmental agents of a chemical, physical and mechanical nature, and re-evaluation of the results on the ultrastructural, histochemical, cytochemical and molecular levels.

3. Studies concerned with mechanisms of cellular and subcellular differentiation utilizing some of the newer techniques available in cell biology (monoclonal immunoglobulins, flow cytometers, recombination of DNA, biotin-avidin systems, use of lectins and other newer techniques to study protein structure and function).

4. Evaluation of the role of gene action in cellular differentiation; study on regulation of gene activity.

5. More intensive studies of gene mutations affecting morphogenesis at gross morphological, light microscopic, fine structural and biochemical levels.

6. Further in vitro studies of embryonic induction, with special attention to correlated ultrastructural, histochemical and biochemical aspects.

7. Correlations between alterations in the basic microstructure and intracellular biochemistry (1) to provide answers to the problems of the origin and development of embryological abnormalities produced by teratogenic substances or mutant genes, and (2) to explore common pathways for teratogenesis and oncogenesis.

8. Studies on the manner in which teratogenic drugs are distributed within the maternal and embryonic compartments, including such aspects as ability to bind, detoxify or excrete a teratogen, and synergistic action.

9. The great importance of genetic disease as a public health problem makes continued and intensified research in this area a high priority. The following selected areas may be identified as needing particular attention for the prevention and treatment of genetic disease in infants and children: (1) Etiology of chromosomal aberrations. The reason for the high frequency of conditions such as Down's syndrome remains unknown. The role of autoimmune factors, viruses, and physiologic factors need further exploration. (2) Identification of high risk mothers for chromosomal aberrations. At the present time, only maternal age can be used to identify women at high risk. Better predictors are needed. (3) Phenotype-genotype interrelation in chromosomal aberrations. The developmental pathogenesis causing the specific malformations and symptomatology of the chromosomal aberrations is unknown. Understanding may lead to possible treatment. (4) Human gene maps — linkage. Accurate mapping of human genes is important, theoretically and also practically, in order to allow intrauterine diagnosis of genetic disease by linkage to marker genes. (5) Developmental genetics. The role of genes in controlling development needs considerably more work. Since most birth defects have a genetic predisposition, the action of various individual genes in organ development needs exploration. Further work in this area also may help in elucidation of dominant gene action which is largely unknown. (6) More rapid culture techniques following amniocentesis. Several weeks are required now before examination is possible of cells obtained following uterine diagnosis. More rapid culturing techniques are required. (7) Improved heterozygote detection. In some autosomal recessive and X-linked diseases, heterozygotes can be detected. Improved techniques are required for genetic counseling, screening, and intrauterine diagnostic programs. For example, a method that would allow heterozygote homozygote detection of cystic fibrosis pre- and postnatally would lead to eradication of this disease. (8) Research in basic genetics. Most all advances in human genetics have been built upon research in basic genetics.

10. Determination of the threshold exposure of physical agents to the developing embryo at various stages of development.

11. Research dealing with the nature and mechanisms that determine the control over total cell number in tissues, organs and organisms at various stages of development. What is the significance of a permanent reduction of cells to the ability of an organism to adapt and function normally?

12. The etiology of some childhood and adult malignancies may be related to intrauterine exposure to some environmental factors. It is extremely important to determine the spectrum of intrauterine pathological events that may lead to the occurrence of malignancy later in life. Therefore, our understanding of the mechanism and impact of transplacental carcinogens should come from both laboratory research and epidemiological studies. This would include studies dealing with the association of mutagenesis, carcinogenesis and teratogenesis as well as the synergistic effect of multiple environmental factors on these events. In an effort to understand childhood malignancies, experimental genetic models and transplacental carcinogenic models in animals should be developed.

13. Experiments in radiation biology and embryology must be performed in order to understand the mechanisms of radiation injury and repair in rapidly developing tissues and the environmental factors that can augment or hinder repair. Similar studies are needed for the evaluation of other forms of electromagnetic radiation (microwave and ultrasound).

14. The use of animal models to study teratogenesis, fetal growth retardation and fetal drug metabolism is an admirable goal. But the information obtained from animal models is only applicable to the human when an understanding of the mechanism of teratogenesis or the metabolism of the drug in the animal and human is well understood. Thus, research in mechanisms of teratogenesis and metabolism of drugs and chemicals is an essential prerequisite for the development of valid animal test systems. The interaction of drugs in combination, or drugs with other environmental agents, is in an area that needs to be studied. The lack of knowledge pertaining to drug and chemical interactions is compounded by the fact that our understanding of fetal and perinatal pharmacology is far behind other fields of pharmacology. The determination and characterization of drug and chemical receptor sites in the developing embryo will assist in clarifying their potential embryotoxicity.

15. There are numerous questions concerning the biochemistry and physiology of the embryo, fetus and perinate that need to be answered: control of parturition; sugar, fat and protein metabolism at different stages of development; mechanisms of thermogenesis; role of fetal, placental and maternal hormones; control of enzyme induction; control of fetal growth; placental perfusion; immunologic development; sex, as it relates to physical and emotional development; specific metabolic features, such as bilirubin metabolism, lecithin synthesis, etc. It also is extremely important to understand all of the above phenomena in abnormal situations, such as exposure to environmental hazards or the presence of maternal disease.

16. Experimental studies dealing with environmental hazards to the embryo and fetus should be extended into the postpartum period. Neurophysiologic and neuropathologic abnormalities may be sensitive measures of intrauterine hazards, such as radiation, chemicals, drugs and infections. But the quantitative and qualitative aspects of these hazards have to be documented in as yet to be determined experimental models.

17. Development of methods of evaluating the status of the central nervous system in the neonate with a degree of certainty that would assist the clinician in determining the prognosis. The evaluation techniques could be in the area of clinical neurology, developmental evaluations or in electrophysiological measurements, which could be correlated with the final development level attained by individual infants.

18. Pregnancy diagnosis has been simplified in the past decade, but the diagnosis still is impossible in the first 2 weeks of pregnancy. The ability to diagnose pregnancy within the first 2 weeks, and even during the first few days, would simplify the clinician's ability to manage potentially pregnant women with regard to drug therapy, radiation exposure, etc. Simple rapid tests for the determination of the exact stage of the estrus cycle, whether ovulation has occurred, and whether pregnancy could be diagnosed closer to the time of conception.

19. Development of techniques to obtain information about the status of the developing fetus that involves no or minimal hazard to the fetus for the purpose of diagnosis, treatment or information gathering. When possible, electronic noninvasive techniques and instruments should be developed and utilized. Instruments for tissue and fluid sampling should be developed. Automated microprocedures should be developed for biochemical, cytogenetic and histopathological analysis.

20. Expansion of ongoing epidemiological surveillance programs for population monitoring, cluster analysis and the evaluation of alleged teratogenicity of environmental agents.

21. Since bleeding in the perinate is a serious consequence of many diseases and treatments in the perinatal period, a better understanding of the hemostatic homeostasis of the perinate is needed. With this knowledge, preventive and therapeutic measures may be developed.

22. A better understanding of the epidemiology of infectious disease in the nursery situation must be developed, if we are to reduce the morbidity and mortality of infections in the nursery situation.

23. The successful prevention and treatment of embryonic and fetal infections will depend upon (1) the development of vaccines to prevent infection in the mother and embryo, (2) the discovery of new infectious agents that affect the embryo, (3) the ability to diagnose adequately the existence of intrauterine infection, (4) the use of serodiagnosis in the perinate to diagnose specific intrauterine infections with simple rapid tests, (5) the development of therapy and prophylaxis for known intrauterine infections, and (6) rapid simple techniques for diagnosing maternal infections.

24. Determine the nutritional requirements of the fetus and neonate and those situations that interfere with adequate nutrition. The role of prenatal and perinatal nutrition in diseases of later life has just begun to be explored.

25. Basic and clinical research dealing with the impact of fetal or maternal therapy on the developing human are essential, since we have only minimal information in this area specifically referring to infant mortality and maternal morbidity and mortality. Proper counseling is dependent on giving accurate information to prospective mothers. There is so little information dealing with the developmental status of children derived from pregnancies in which the mother had a particular disease, that proper counseling frequently is impossible. Thus, evaluation of the effect of maternal disease, environmental exposures, or environmental situations should include long-term evaluations of growth, development, intellect, behavior and certain diseases, such as tumors. The situations to be evaluated include (1) medical diseases in the mother; (2) environmental exposures during pregnancy, such as drugs; (3) drugs and procedures utilized during labor, such as anesthetics, pitocin induction, delivery position, etc.

26. Clinical research to determine the impact of spontaneous and various forms of induced abortion on future conception and future pregnancies. This evaluation should include the developmental status of the offspring and not just the perinatal mortality of future pregnancies.

27. Long-term predictive studies are needed to differentiate between environmental effects on behavioral development and effects of identifiable antenatal, perinatal and neonatal risk factors. Obstetrical and neonatal management techniques must be specified and standardized. Observations are required of immediate, as well as longer term, effects of interference with the establishment of the early mother-infant relationship. Differences among families, as well as mothers, representing the nurturing environment, must be specified in terms of psychological styles, socioeconomic status and related to outcome. These variables require careful delineation, if we are to examine the impact of the transactional effect between child and family. There is also a need for refined and reliable measures of the components of *psychologic stress*, which must be specified and controlled, particularly to allow predictive studies of behavioral influences on pregnancy and subsequent development of the child.

28. Studies should be undertaken to determine the kinds and magnitude of the family burden of a congenitally malformed member, including the effects on health and psychologic functioning of parents and siblings, on intrafamilial relationships and on the stability of the marriage.

29. Evaluation of the impact of public education on the quality of health care and the appropriateness of services sought by the public. We require information about effects of dissemination of information on a large scale. This requires experimentation with a variety of educational techniques, relating to reproductive attitudes and practices and public attitudes toward defective individuals.

30. Studies of hazards and effectiveness of genetic counseling. The measurement of the results of a clinical interpersonal encounter, such as genetic counseling, is a complex task.

31. The factors responsible for the onset of labor – both normal and premature labor.

32. Evaluation of the rightful place of perinatal monitoring in obstetrical care. Included in the evaluation must be the efficacy, simplicity, safety and cost. Furthermore, morbidity and mortality are not satisfactory criteria for this evaluation. Physical and mental development during childhood are far more important than perinatal mortality in assessing the assets and liability of perinatal monitoring.

33. Establishment of research programs to evaluate competitive methods used in assisting childbirth. The following techniques or procedures are used by various groups. Their place in optimal health care is accepted by some; rejected by others. Only properly controlled studies will determine their overall benefit or hazard to the mother and the developing offspring.

Summary

The problem of birth defects has consumed a greater portion of our health care resources because of the reduction of infectious diseases and our ability to salvage and care for many malformed children. These health care costs are estimated conservatively at \$20 billion per year.

For every 1350 conceptions there will be 1000 live born, of whom 130 will have genetic or anatomical defects. It is true that many of the genetic defects will not manifest themselves until years later, but many of the anatomical defects will be diagnosed in the neonatal period. A genetic etiology accounts for 25% of anatomical defects (5% cytogenetic, 20% autosomal). The largest group (65%) is believed to be polygenic or multifactorial in origin, although a large portion of this group may be spontaneous intrinsic developmental defects or simply due to unknown causes. Known environmental factors account for only 10% of anatomical malformations, but many of these are due to preventable causes (maternal disease states; maternal infections; intrauterine constraint and constriction problems; and drugs, chemicals, irradiation, hyperthermia). Many physicians and lay individuals are confused about the etiology of birth defects, attributing a much higher proportion to drugs, chemicals and X-irradiation.

Advances in the Birth Defects Field in the Past Decade

The development of the Congenital Malformation Surveillance Branch of the Center for Disease Control has been an important contribution to our understanding the incidence of congenital malformations and for testing various hypotheses.

A number of agents were demonstrated or reconfirmed to be embryotoxic for the human:

- 1) Warfarin (Warfarin syndrome)
- 2) Diethylstilbesterol (Adenosis, associated adenocarcinoma of the vagina)
- 3) Diphenylhydantoin (Hydantoin syndrome)
- 4) Tridione
- 5) Alcohol and cigaret smoking (reconfirmed)

Other agents were suggested to be teratogenic or embryotoxic, but the effect is either nonexistent, associated but not causal or associated but rarely causal. Thus Valium, meprobamate and certain progestational agents fell into this category. Other alleged teratogens that are not associated with birth defects in the human are imipramine, Bendectin and meclizine.

Better management of pregnant women with serious disease has permitted them to become pregnant, thus increasing the neonatal morbidity. The creation of the high risk group of patients has focused attention on an important group of patients. Advances in amniocentesis, fetoscopy, fetoprotein analysis, ultrasonography, enzyme and biochemical determinations permit both diagnosis and treatment very early in gestation. The training of subspecialists in obstetrics (perinatologists) and pediatrics (neonatologists), as well as the routine use of Rhogam and the induction of lung maturation has increased neonatal survival. The improvement in morbidity, mortality and prognosis, following the surgical correction of anatomical malformations, has been dramatic.

The emergence of the Group D beta streptococcus and the reporting of other teratogenic viruses offers new but potentially controllable problems. Many intrauterine infections are still diagnosed too late or are untreatable. Hyperthermia and mechanical factors again have been suggested as rare causes of malformations. The field of

genetics has made giant strides in the area of chromosome analysis, gene location, heterozygote identification, intrauterine diagnosis and suggestions for intrauterine therapy.

Advances in the birth defects field have moved very fast resulting in diagnostic and therapeutic measures that present psychological, ethical and legal dilemmas. Social scientists may study the development of these controversies and discussions about abortion, the rights of the fetus, the impact of birth defects on the family unit, fetal therapy and fetal research, and may be able to offer some advice. For the most part, the solutions of these dilemmas will be derived from complex interactions in the social arena and will not be solved by the scientific community alone.

The next decade should bring further advances in the birth defects field. As always, we rely on a substantial foundation of basic science research in many areas of reproductive biology. Important new techniques that will assist the basic scientist in unraveling the mysteries of embryonic development include studies in individual cell function and differentiation (flow cytometry, embryo culture), identification and characterization of proteins (separation science, lectin use, monoclonal immunoglobulins), and gene action and function (recombinant DNA). The potential of basic research is even greater as new tools permit us to ask questions that previously were unanswerable.

The application of computers to both basic and clinical research has made the scientist more productive. This is obvious in the fields of genetics, syndrome delineation, and ultrasound diagnostic equipment. In other areas, only minimal information has developed. This is particularly true of nutrition, in spite of the fact that this is an area that has been superficially emphasized. But nutrition knowledge is only as useful as the soundness of the biochemistry on which it is based. Much of nutrition teaching is dogma based on tradition and bias, a reflection of how much more research is needed in this area.

The improved management of maternal disease states and the development of vaccines or effective treatment of intrauterine infections are areas for maximal investment of resources.

In summary, there are many investigative areas to concentrate our energies in the next decade, in order to decrease the incidence and better manage the problem of birth defects. Social and political issues will be involved intimately in determining which options will be selected. (It is very likely that advances in birth defect research and genetic research will permit us to determine, with great accuracy, the developmental status of every developing human embryo.) At the present time, our psychological and social development has not proceeded to the point where we know how we will utilize this information.

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